Appendix 5-A

Summary of LeadSpread and IEUBK

Evaluation of Methodologies for Lead Standards

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U.S. EPA programs now primarily rely on the U.S. EPA's Integrated Exposure Uptake Biokinetic (IEUBK) model to estimate blood-lead concentrations in children because of exposure of children to lead in the environment. The IEUBK model does not consider direct exposure to paint. Other models considered by the EPA for the Section 403 rules (see FR 63(106):30317, June 3, 1998) were the multimedia model using the Rochester Lead-in-Dust Study and an empirical model (i.e., performance characteristic model) also using the Rochester data. The multimedia model was used only for household dust with only dripline soil lead measurements. The empirical model was used where both soil and dust lead levels were of concern. Both the IEUBK model and the multimedia model employed a GSD of 1.6.

For guidance in the school sites program, California has proposed to use a much more simplified spreadsheet approach using a program named "LeadSpread". The primary differences between the IEUBK model and LeadSpread are that the IEUBK model is a simulation model with a biokinetic component that predicts blood lead concentrations in children over time whereas LeadSpread is a regression-based model in that blood lead concentrations are linearly related to exposures. These approaches will be contrasted in the following discussion.

LeadSpread, Version 7:
This Microsoft Excel-based program calculates concentrations of lead in blood in adults and children based on five exposure pathways: dermal contact with site soil/dust, ingestion of site soil/dust, background air inhalation, dust inhalation from a site, ingestion of drinking water, ingestion of market basket food, and ingestion of home-grown produce. For the ingestion route of exposure, blood lead concentrations are calculated using proportionality constants (child and adult) between the amount of lead ingested per day and the blood lead concentration. Similar proportionality constants are employed for the inhalation and dermal contact routes of exposure. The model user is directed to only make changes in the following site-specific and background data: background lead concentration in air, lead concentration in site soil/dust, lead concentration in drinking water, percentage of ingested produce homegrown, and respirable soil/dust from site ($\mu g/m^3$). The authors of the model do not recommend that the user modify any of the other critical variables, such as the proportionality constants, bioavailability factors, the quantity of media that the child is exposed to per day, and duration of exposure. All contributing sources to blood lead concentrations are then summed. The summed value is then defined as the geometric mean. A fixed value for the geometric standard deviation is imposed (1.6) and various percentiles of the distribution of expected blood lead levels for the overall blood lead concentration are calculated. By fixing all inputs but soil lead concentration, the soil lead level estimated to

be associated with a limit of 10 µg/dL of lead in blood at a specified percentile of the above distribution can be calculated.

IEUBK Model:

The IEUBKwin is a stand-alone computer program that requires an IBM compatible PC running under the Windows-based operating system. An earlier version ran under the MS-DOS operating system. The new Windows-based version is more user-friendly and allows more output options. The two programs are otherwise identical. This program calculates a lognormal probability distribution of blood lead concentration in children who have been exposed to various environmental media (air, soil, dust, and diet). Other output options are also available. The model has four functional components – exposure, uptake, biokinetic, and probability distribution (Figure 1):

- Exposure Component. The exposure component calculates media specific contact rates based on media-specific consumption rates. Data requirements are the concentrations of lead in various environmental media to which the child is exposed, the quantity of media that the child is exposed to per day, and duration of exposure. The media include air, soil, house dust, drinking water, and food. Media intake rates are media- and age-specific.

- Uptake Component. The uptake component calculates the amount of lead inhaled or ingested that is transferred to the blood plasma. The model allows the user to input bioavailability fractions (the fraction of inhaled or ingested lead that is actually transferred onto the blood plasma) over the model default fractions. Absorption factors are age- and media-specific. At higher doses, the absorption fractions are modified to account for saturation effects.

- Biokinetic Component. The biokinetic component models the transfer of blood between plasma/extracellular fluid and various organs and excretion pathways (urine, feces, skin, hair, and nails). Mass transfer coefficients govern transfer rates among compartments.

- Variability. The probability distribution component calculates the lognormal probability distribution for the calculated blood lead concentration using a default geometric standard deviation of 1.6.

The following outputs can be selected in an IEUBK run: Geometric blood lead concentrations by age, percent of children with blood lead levels exceeding a specified level of concern, average media-specific daily lead uptake rates, and media-specific remediation goals. Output can be saved and presented as tables, graphs, or text files.

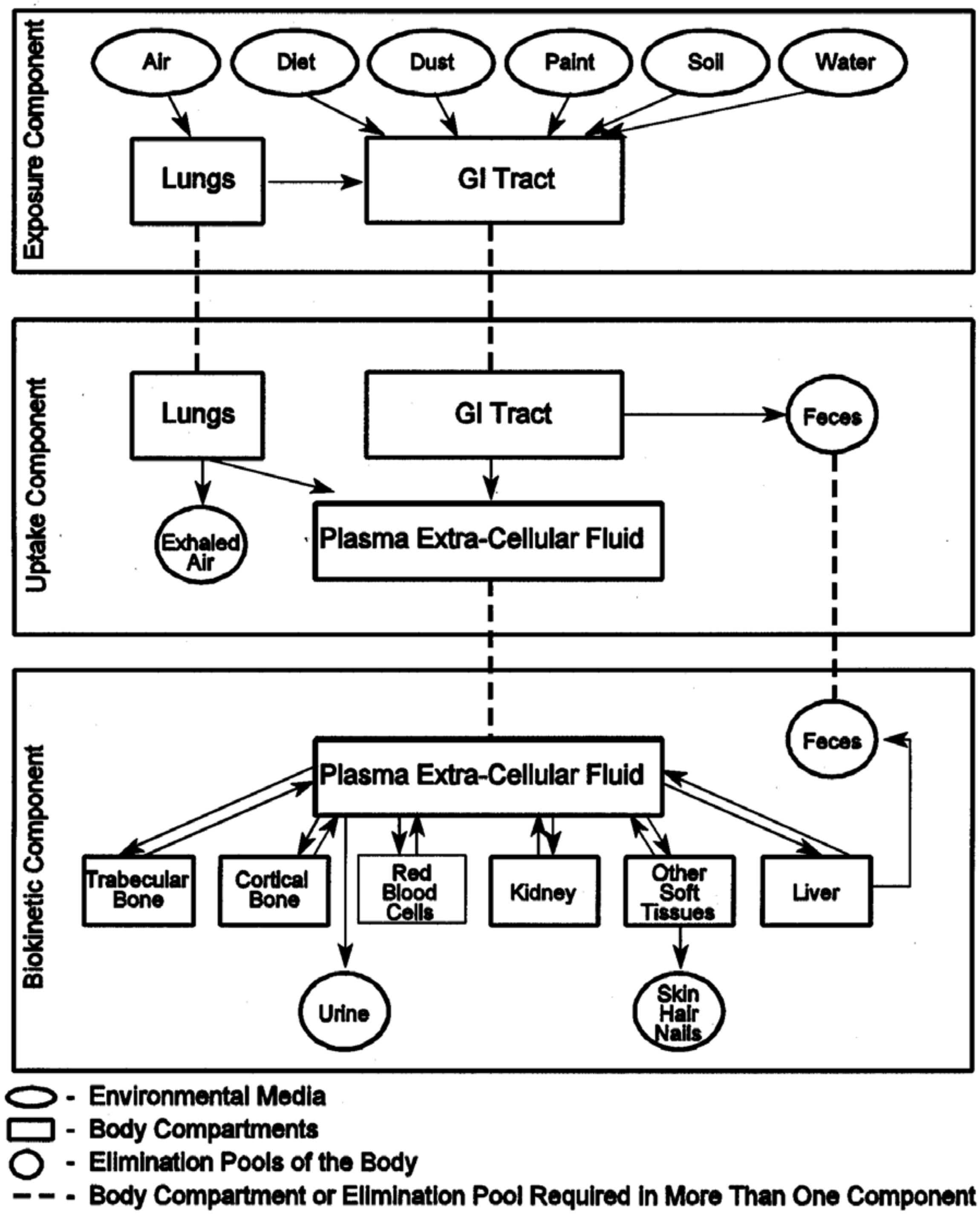

Figure 1. Structure of the IEUBK model.

General Discussion

Model Structure:
LeadSpread is a spreadsheet-based model using simple linear algebraic equations. Adjustment of input parameters results in an immediate recalculation of output values. In contrast, the IEUBK is run as a batch program after input values are set and the application mode is set. Both models are deterministic in that all input values are fixed. Although similar in respects to estimating exposure of children to lead from various media sources, the IEUBK model provides extensive modeling of the transfer of lead among biological tissues and its elimination from the body using numerical methods with specified time steps. The heart of the IEUBK model is the biokinetic component in which changes in the mass of lead in various tissue compartments are modeled with differential equations. Concentrations of lead in blood are calculated for specified time steps using the backward Euler numerical method. Unlike LeadSpread, the IEUBK models changes in time (zero to 84 months of age) of lead concentrations in various bodily tissues, including blood. Limitations of the regression-based approach (i.e., using slope factors) used in LeadSpread were pointed out by the EPA (1994) which stated the following:

(1) "Slope factors are a function of many factors: media ingestion rates; bioavailability and absorption of lead from the medium; and biological kinetics of lead retention and elimination in the child. Biological and physical differences between sites and study populations cannot be incorporated explicitly and quantitatively into regression slope factors from different studies.

(2) "Slope factors for a single medium, such as lead in air or lead in soil, may provide only a very incomplete picture of total lead exposure from a particular source, even if the source is identified with the medium. A single medium such as household dust may contain lead from many sources, and lead from a single source such as exterior lead-based paint may contribute to several exposure media pathways to the child."

Model Inputs:
Like LeadSpread, the IEUBK model allows for the input of lead concentrations in soil, water, and air. Unlike LeadSpread, the IEUBK model is much more flexible in that it allows for the user input of 46 parameters. Some of these parameters are age-specific. Unlike LeadSpread, the IEUBK model distinguishes between outdoor soil and indoor dust. LeadSpread is especially conservative in that it recommends that the input soil lead value be the upper confidence limit of the mean soil lead concentration whereas the IEUBK model documentation recommends using a simple arithmetic mean of soil concentration from a representative area in the child's yard (U.S. EPA, 1994a). The significance level for the confidence limit is not specified in LeadSpread. Unlike the IEUBK model, LeadSpread considers dermal absorption and dust inhalation. Although it does not explicitly consider these routes of exposure, the IEUBK model allows for user determined alternate sources of exposure. These pathways were not explicitly included in the IEUBK model because of their minor contribution to overall lead burden in

children. The IEUBK model also considers the maternal contribution to a newborn's blood lead concentration at birth. A comparison of IEUBK and LeadSpread exposure and uptake variables is provided in Table 1.

Both the IEUBK model and LeadSpread incorporate default bioavailability factors for various exposure media (e.g., water, food, dust). Although DTSC does not want the user to adjust these factors in LeadSpread, adjustment of these factors is allowed in the IEUBK model if the user has adequate information supporting alternative factors. One of the most variable factors is that for bioavailability of soil lead, in that soil particle size and chemical form of lead may have great influence on the bioavailability fraction. The IEUBK default bioavailability factor for soil lead is 30% compared to 44% for LeadSpread. Whereas LeadSpread relied on one study using rats to set the bioavailability factor, the EPA based its estimates on extensive research, allowing the user to adjust this parameter as necessary. Further, the IEUBK allows for the future use of *in vitro* physiologically-based extraction tests to estimate the bioavailability factor.

Table 1. Default exposure variables and parameters for children.

Variable or parameter	*IEUBK model*	*LeadSpread 7.0*
Source parameters		
Concentration of lead in air (µg/m^3)	User specified (0.10)	User specified (0.028)
Ratio of indoor to outdoor air lead concentration	User specified (0.30)	Not included
Concentration of lead in drinking water (µg/L)	User specified (4.0)	User specified (15.0)
Concentration of lead in soil (µg/g)	User specified (200)	User specified
Concentration of lead in dust (µg/g)	User specified (200)	Not included
Soil ingestion as a fraction of total soil and dust ingestion	0.45	Not included
Mass fraction of soil-derived dust in house dust	0.70	Not included
Skin area (m^2)	Not specified	0.29
Soil adherence (µg/m^2)	Not specified	0.02
Concentration of lead in market basket food (µg/Kg)	See under intake rates	3.1
Concentration of lead in home-grown produce (µg/Kg)	See next row	114.8
Concentrations of lead in home grown fruits and vegetables; game fish and meats (µg/g)	User supplied (0)	Not specified
Fraction home grown produce	See under intake rates	User specified (0.07)
Fraction of fruits and vegetables homegrown; fraction of fish and meats from fishing and hunting	User supplied (0)	Not specified
Respirable dust (µg/m^3)	Not specified	1.5
Time outdoors (hrs/day)	1 to 4*	Not included
Intake rates		
Breathing rate (m^3/day)	2 to 7*	6.8
Drinking water ingestion rate (L/day)	0.20 to 0.59*	0.4
Food ingestion rate (Kg/day)	Not specified	1.1
Dietary lead intake rate (µg/day)	5.53 to 7.00*	Calculated
Soil ingestion rate (g/day)	0.085 to 0.135*	0.1
Soil ingestion rate, pica (g/day)	Optional	0.2

*Age specific values

Risk Assessment:
Both models are designed to evaluate individual risks, i.e., the probability that a child who will have a blood lead concentration that equals or exceeds 10 µg /dL, given certain environmental media concentrations of lead.

Model Applications:
Although both models calculate the percent of children with blood lead levels exceeding a specified level of concern, only the IEUBK model can (1) simulate changes in blood lead concentrations with age of the child, (2) calculate average media-specific daily lead uptake rates, and (3) calculate media-specific remediation goals. Output from the IEUBK model can be saved and presented as tables, graphs, or text files.

Model Validation:
As part of its validation strategy, the IEUBK model development team (U.S. EPA, 1994) considered:

(1) The scientific foundation of the model structure, i.e., does the model adequately represent the biological and physical mechanisms of the modeled system?
(2) Adequacy of parameter estimates, i.e., how extensive and robust are the data used to estimate model parameters.
(3) Verification of the computer code.
(4) Empirical comparisons of model predictions with observational data.

The scientific foundation of the IEUBK model is described in a guidance manual (U.S. EPA, 1994). Parameter estimation methods are fully described in a technical support document (U.S. EPA, 1994). Coding was verified by comparison with coding in another programming language. Protocols for validation studies were described by the TRW (1994). Calibration and validation of the model was partially based upon empirical data from the "Rochester Lead-in-Dust Study." The IEUBK model was further calibrated against environmental-lead and blood-lead data from two western communities and urban sites (see FR 63(106):30319, June 3, 1998; and U.S. EPA, 1998).

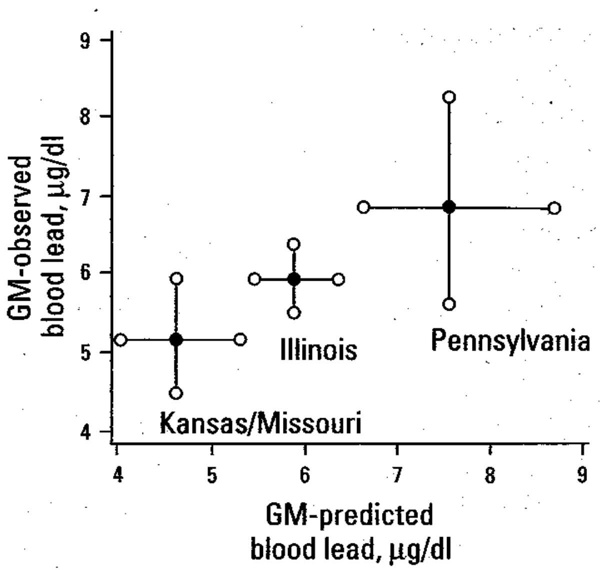

Figure 2. Comparison of geometric mean predicted and observed blood lead concentrations by site.

Model validation studies were conducted by Hogan et al. (1998) using three epidemiological datasets of children between zero and 7 years of age. In the validation process, the authors used residence-specific environmental lead measurements from these data sets and compared the geometric mean predicted blood lead levels to the actual geometric mean blood lead levels in the three populations of children living in these residences (Figure 2). Differences between predicted and measured geometric means for the three populations ranged from zero to 0.7 μg /dl. Differences between observed and predicted probabilities of exceeding 10 μg /dl ranged from 2 to 4 percent. The IEUBK model was also evaluated using subpopulations of these children based upon age, time away from home, time spent outside, food taken outside, locality, and presence of lead-based paint. Due to insufficient sample sizes or other factors, conclusions could not be easily drawn based upon these subpopulations. There are no comparable validation studies for LeadSpread.

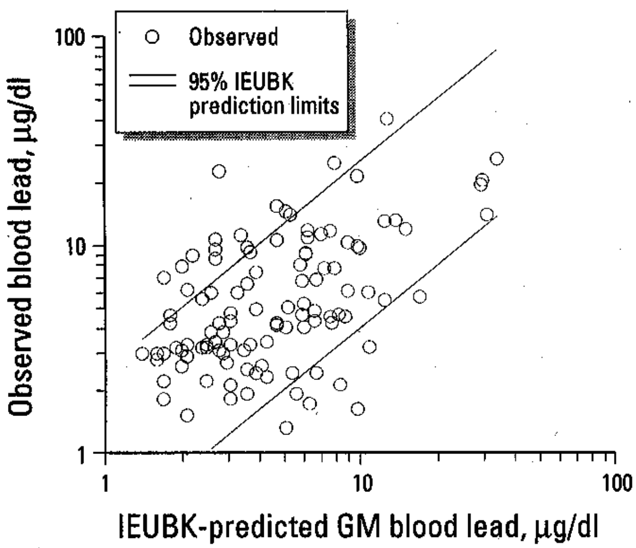

Figure 3. Comparison between individual predicted
and observed blood lead concentrations for
Kansas/Missouri children.

Although not intended to predict blood lead concentrations in individual children, Hogan et al. (1998) plotted the logarithms of individual blood lead measurements against the logarithms of predicted blood lead levels. Although the mean predicted blood lead levels closely corresponded to the measured mean blood lead levels for each of the three populations, there appeared to be no clear linear relationship between individual predicted and measured blood lead concentrations (see Figures 3 through 5). There are no comparable validation studies for LeadSpread.

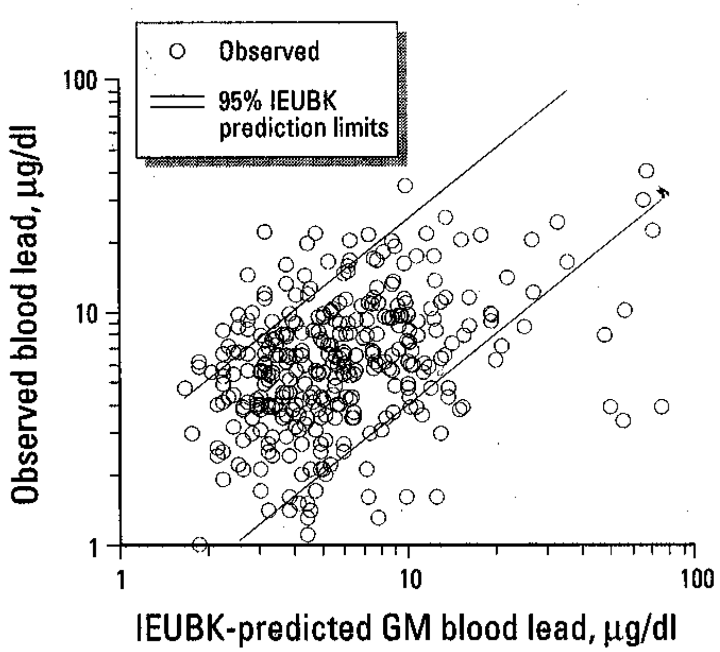

Figure 4. Comparison between individual predicted and observed blood lead concentrations for Illinois children.

A useful measure of the practicality of the IEUBK model would be to determine the fraction of all blood lead measurements exceeding 10 µg /dl that corresponded to predicted values less than 10 µg /dl. In Figures 3 to 5, this fraction would be the number of points in the upper-left quadrant of a graph divided by the total number of points in that graph. A high fractional value would suggest that the model might not be sufficiently protective.

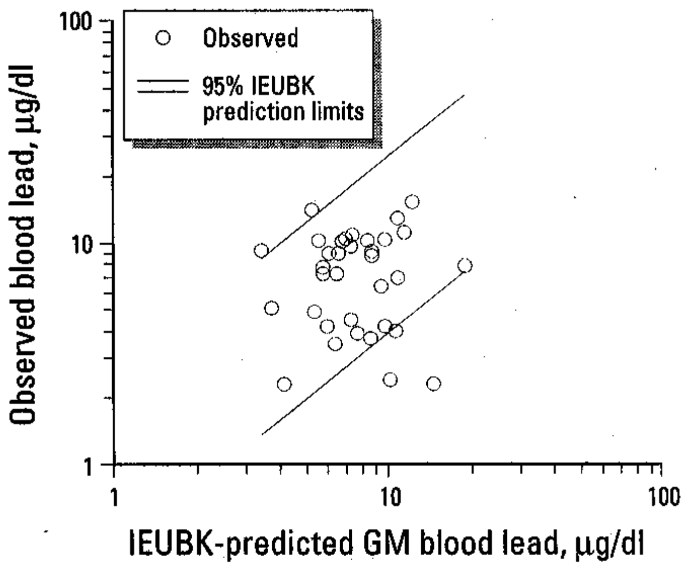

Figure 5. Comparison between individual predicted and observed blood lead concentrations for Pennsylvania children.

That models of environmental processes (e.g., the IEUBK model) can be validated at all has been called into question by Oreskes (1998). She points out that all models are subject to four categories of flaws: theoretical, empirical, parametrical, and temporal. To the temporal flaws, one could also add spatial flaws. Theoretical flaws occur when the model does not adequately describe in mathematical terms the physical processes being modeled. Empirical flaws address quality of measurements of model parameters. Parametric flaws result from the simplification of input parameters. Temporal (and spatial) flaws occur when it is assumed that the modeled systems are stable in time (and space). Neither LeadSpread nor the IEUBK model can be said to be free of all of these flaws. Oreskes argues that one should address “means of evaluation” rather than validation strategies. She notes it is better to articulate a model’s uncertainties than to proclaim its validity.

Sources of Uncertainty:
Uncertainties can be divided into those that are generic (e.g., biokinetic parameters) and those that are site-specific (e.g., amount of soil ingested, concentration of lead in ingested soil, fraction of ingested lead that is absorbed from the GI tract, variations in exposure in space and time), and individual behavior patterns.

The greatest uncertainty in modeling childhood lead exposure appears to be from soil and dust ingestion and uptake factors, in particular, the amount of soil ingested and lead absorption rates. Other major sources of uncertainty are the representativeness of the sampled soil and household dust to that being ingested and the different behavior patterns of children. Much of this uncertainty may be reduced by taking more representative suites of soil samples, and by estimating the fraction of lead that is bioavailable using a physiologically based extraction test.

Model Documentation:
The IEUBK model is extensively documented (U.S. EPA, 1994a and 1994b; and U.S. EPA, 2001a and 2001b). It is based upon an extensive body of research and is supported by most of the major EPA programs. In contrast, LeadSpread provides pop-up windows within the Excel spreadsheet explaining model variables. Equations used are transparent in that they can be seen by selecting the appropriate cell.

The Bioavailability Fraction for Soil Ingestion

The EPA has defined bioavailability as "the fraction of the total amount of material in contact with a body portal-of-entry (lung, gut, skin) that enters the blood" (U.S. EPA, 1994). The EPA also distinguishes between absolute bioavailability and relative bioavailability. **Absolute bioavailability** is the amount of a substance entering the blood via a particular route of exposure divided by the total amount administered. **Relative bioavailability** is the bioavailability of a particular substance relative to a reference material (e.g., lead acetate). Both LeadSpread and the IEUBK model use absolute bioavailability.

Factors affecting lead absorption: Adsorption is affected by properties of the ingested media containing lead, such as particle size and mineralogy. It is also affected by the surrounding environment, including pH of the stomach and intestinal tract, the composition of gastric juices, and co-ingested food. As such it is almost impossible to predict blood lead levels based upon ingested lead. The IEUBK model uses a default value of 30% for ingested soil lead in young children and LeadSpread uses a default value of 44%. The IEUBK uses a default absorption fraction of 50% for food and liquids.

Few studies have measured blood lead concentrations in animals subject to controlled exposures. Because of ethical considerations, only a few studies have measured blood lead levels in children where the level of exposure to dietary lead was also known (Ryu et al., 1983; and Sherlock and Quinn, 1986), but never purposefully administered. The Sherlock and Quinn data show increasing blood lead concentrations with increased lead intake with the rate of increase decreasing with increasing intake (see Figure 2 of White et al., 1998).

Casteel et al. (1997) investigated the bioavailability of soil lead in juvenile swine and observed a range of bioavailability for different soil/lead matrices. Steele (1998) noted that soil particle size, mineralogy, and lead speciation influenced bioavailability.

Ruby et al. (1993) developed an *in vitro* physiologically based extraction test to simulate chemical reactions occurring in the gastro-intestinal tract. Using seven different lead bearing matrices, Ruby et al. (1996) has shown a linear correlation ($r^2 = 0.93$, $n = 7$) between *in vitro* and in vivo from a Sprague-Dawley rat model. Evidence is also available showing good correlation with *in vivo* data using swine (Ruby et al. (1999). A simplified version of the *in vitro* test is currently being evaluated.

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